RESEARCH ARTICLE

Pitfalls in Reimbursement Decisions for Oncology Drugs in South Korea: Need for Addressing the Ethical Dimensions in Technology Assessment

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Abstract

This study aimed to discover to what extent ethical issues are considered in the reimbursement decision process based on health technology assessment (HTA) in Korea, especially for oncology medications. Public summary documents (PSDs) published by the Health Insurance Review and Assessment Service (HIRA) were analyzed for empirical and normative factors. For external comparison, PSDs presented by corresponding institutions of Australia and the United Kingdom were employed. Furthermore, the opinions of eight expert oncologists were obtained regarding the accountability of the evidence in PSDs. Among 7 oncology drugs, there were differences in the final decisions and empirical factors considered, such as selected comparators and interpretation of evidencebetween the PSDs from the three institutions. From an ethical viewpoint, the following matters were deficient in the HTA decision-making process for oncology drugs: clear and reasonable standards; identifying and evaluating ethical values; and public accountability for reasonableness about decisions and due process.

Keywords: Health technology assessment - ethics - economic analysis - cost-effectiveness analysis - Korea

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Introduction

To measure the health benefits of innovative pharmaceuticals, health technology assessment (HTA) methods are useful when making insurance coverage decisions (M. F. Drummond et al., 2008). For the purpose of containing pharmaceutical expenditures, a positive listing system of reimbursable drugs was introduced in December 2006 under the Drug Expenditure Rationalization Plan in Korea. Under this policy, pharmaceutical manufacturers submit clinical and economic evidence of a new drug to the Health Insurance Review and Assessment Service (HIRA) in their reimbursement applications. After HIRA approves the listing the new drug moves to the next phase of negotiating its final price with the National Health Insurance Corporation. Most pharmaceutical companies have expressed concerns over this policy, arguing that it may exert a negative effect on the development of new innovative drugs by favouring cheaper drugs over novel drugs, that, although expensive, provide reasonable value for the cost (Kwon, 2009). The presence of a limited number of experts to carry out, interpret, and evaluate such economic outcomes has also aggravated the worries of pharmaceutical companies in Korea. However, following the economic climate prevalent in single-payer health systems, most global and local pharmaceutical companies have come to agree on the need to provide cost-effectiveness outcomes to the payer (Yang, 2009).

In an effort to rapidly implement HTA, both pharmaceutical companies and HIRA in Korea have been emulating the organizational and methodological experience of established HTA systems such as those in Australia, Canada, and the United Kingdom (UK) (Kamae, 2010; Oortwijn et al., 2010). Based on the critical assessment conducted by HIRA, the Drug Reimbursement Evaluation Committee (DREC), consisting of representatives from medical associations and consumer interest groups, determines whether to fund the drug. According to HIRA guidance, technical factors DREC should consider are: (i) the availability of therapeutic alternatives and indispensability in the clinical setting; (ii) clinical effectiveness; (iii) cost-effectiveness; (iv) budget impact; and (v) the listing situation of the drug in other countries (Health Insurance Review and Assessment Service (HIRA), 2007).

As in other countries, no arbitrary fixed willingness to pay threshold for accepting incremental cost-effectiveness ratio (ICER) values has been officially designated in Korea. However, the per capita gross domestic product is usually referred to in determining the acceptability

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of ICER throughout DREC's decision making-process (Yang, 2009). Although interpreting the ICER measure seems relatively simple, explicit, and even transparent, it creates a conceptual problem in terms of vertical equity over equality (Schlander and Beck, 2009; Hauck and Tsuchiya, 2011). For example, the initial health states of individuals are not directly considered (Schlander and Beck, 2009). Furthermore, valuation related to loss of quality of life may also vary across different age and disease contexts (Weinstein, 1988). Accordingly, ICER evidence-based reimbursement policies have been criticized for limiting access to new novel treatments, which are typically modestly effective but extremely expensive, especially for cancer patients (Low, 2007; Rocchi et al., 2008; Schnipper et al., 2010). In fact, while oncology drugs seem to have a higher threshold of acceptability compared with non-oncology drugs by decision-makers, those with higher ICER values have been associated with constrained access and slower time to coverage in HTA systems (Rocchi et al., 2008; Chim et al., 2010).

In addition to evidentiary and scientific values, responsible decision-makers should make judgments using non-evidentiary and ethical values in a context-sensitive approach to determine what is good for society (Rawlins and Culyer, 2004; Burls et al., 2011). Moreover, people will accept drug coverage decisions only if they are assured that the rationales for the limits to new drug therapies are relevant to the society's needs under a fair and transparent decision-making process (Daniels et al., 2003; Drummond et al., 2009). Although ethical considerations are the inherent notion of HTAs, it has been argued that the present HTA evaluations do not sufficiently reflect the ethical implications in the HTA process, even in the HTA-leading countries (Hofmann, 2008; DeJean et al., 2009).

With this background in mind, we aimed to discover to what extent ethical values were prudently considered or addressed in the reimbursement decision process. For this purpose, we systematically analyzed public documents for DREC's reimbursement decisions regarding oncology drugs in Korea.

Materials and Methods

Public summary documents (PSDs) regarding DREC's reimbursement decisions began to be published online at the HIRA website (http://www.hira.or.kr/) in 2011, almost 3 years after the introduction of the positive listing system. The publication was operated from the first dossier completed with a reimbursement decision in the order. For this study, we collected PSDs for cancer drugs published online until April 2011, when the PSDs were downloaded from the HIRA website by the authors. For external comparison of empirical evidence, we searched the corresponding PSDs of the Pharmaceutical Benefits Advisory Committee of Australia (PBAC) (http://www.health.gov.au/internet/main/publishing.nsf/Content/public-summary-documents). If related PSDs were not identified from the PBAC webpage, guidance papers released by the National Institute for Health and Clinical Excellence (NICE) of the UK were obtained (http://www.nice.org.uk/Guidance/TA).

The authors and an analyst scrutinized these PSDs to examine if the evidentiary factors were used with clear relevance and ethical considerations in the decision-making process. The empirical factors evaluated, such as comparators, economic and clinical claims, and other decision contexts, were summarized into tables to allow for a brief comparison between decision-making bodies. Pertinent substances and key points in each decision were also identified and documented by each author. In the same way, the PSDs of PBAC and NICE were summarized by the authors. These summaries were subsequently made into a table for a comparison of PSDs between decision-making bodies.

We invited one or two oncologists per relevant subspecialty (such as leukaemia, breast cancer, and colorectal cancer), for an in-depth interview. This was specifically undertaken to assess the stakeholders' comments or suggestions pertaining to the new oncology drugs submitted to, and reviewed by, HIRA. All eight oncology experts were selected by the recommendation of the cancer centre's chairman at a university hospital, considering the expert's previous experience with clinical research for the purpose of producing input data for the HTA reports. To help the interviewee understand the decisions, each oncologist received his/her subspecialty-relevant summarized table via e-mail one week before the interview. A three- to four-hour interview session was scheduled separately for each of the eight oncologists.

At the beginning of each interview, the authors briefly explained to the interviewee the reimbursement decision process and the values of evidentiary factors on the PSDs. The questions or comments the interviewee brought up about the summaries were answered and discussed. Then, the authors asked questions which were prepared by the authors in advance after having summarized and compared the PSDs. The number of questions varied from four to 13 depending on the issues about the drug and the evaluation contents in the PSDs. For example, the interviewees were asked about their opinions and judgments regarding the needs and utilization changes within the real health care system on the assumption that cetuximab was reimbursed under a risk sharing model, which was the case in PBAC decisions.

In addition to efforts identifying social and ethical considerations (such as equity or historical precedent), the fairness of the decision-making process setting was evaluated by inference from the PSDs. Finally, the authors extracted qualitative key themes among ethical dimensions which appeared to have not received the consideration they may have deserved from the decision-makers.

Results

Reimbursement decisions

Drug reimbursement decisions made from January 2007 to June 2009 were available when the authors drew the PSDs from the HIRA website in 2001. In this period, approximately 100 new drugs were reviewed for reimbursement decisions, including 12 oncology drugs

(Table 1). Among the 12 oncology drug applications, eight were submitted by global pharmaceutical companies, while the other four were submitted by the non-profit Korea Orphan Drug Centre or wholesale trade companies. Data of cost-effectiveness models were included in four dossiers, all of which were developed and submitted by global manufacturing pharmaceutical companies (Table 1).

Starting with dasatinib, five cancer drugs were approved for reimbursement during the period. With the exception of dasatinib, which was listed on the Korean national formulary relatively earlier than in other countries, the other four reimbursement-approved drugs had been listed beforehand in other reference countries during the period of HIRA's review process. According to the PSDs of HIRA, PBAC and NICE had approved coverage for two and five oncology drugs, respectively. Indeed, the statement that "Australia and the UK had not listed cetuximab" in the PSD on the submission for cetuximab suggested that among reference countries, the reimbursement decisions of Australia and the UK were given more weight by DREC.

We identified five public documents of PBAC and two of NICE on corresponding public documents. Tables 2 and 3 summarize the empirical factors considered by HIRA in comparison with PBAC and NICE. Differing recommendations were made by DREC and PBAC for cetuximab and topotecan, for which the decisions of DREC were made earlier than PBAC (Table 2). Fulvestrant and trabectedin were rejected by DREC while they had been under review by NICE (Table 3).

Relevance of empirical factors

Rationale and revision for the ICERs evaluated: All applications reviewed by PBAC presented economic modelling data consisting of cost-effectiveness or cost-utility model analysis data, except nilotinib, which was submitted with a cost-minimization approach. The ICER value of nilotinib was not accepted, and a conditional approval upon agreeing to a weighted average cost of comparators was recommended by DREC, which is essentially the same approach as a cost-minimization strategy (Table 2).

The ICER values usually appeared irrelevant to DREC's confidence as expressed by sentences in the PSDs. Because the ICER value is certainly relevant, a strategy of setting a comparable price rather than submitting pharmacoeconomic modelling data might work more usefully in achieving market positioning with less time and minimal resources consumed in their preparation. Since the comparator had long been criticized for its expensive price in Korea, a reimbursement application for dasatinib was prepared using this strategy. Intuitively, the new drug's lower price would lighten the decision-makers'

Table 1. Oncology Drugs Assessed by the Drug Reimbursement Evaluation Committee (DREC) between January 2007 and June 2009

Oncology drug	Oncology drug	Indication	Sponsor	DREC meeting date	Decision result	CE evidence submission	Reference countries for listing
Sprycel	Dasatinib 70, 50, 20.mg	CML	BMS Korea	Jul 20, 2007	Approval	n/s	n/m
Erwinase	L-asparaginase 10,000 IU	ALL	BL&H	Oct 19, 2007	Rejection	n/s	n/m
Oncaspar	Pegaspargase 3,750 IU/5 mL	ALL	KODC	Oct 19, 2007	Rejection	n/s	n/m
Dacogen	Decitabine 50 mg	Myelodysplastic syndromes	Janssen Korea	Dec 21, 2007 Feb 22, 2008	Approval	n/s	US
Erbitux	Cetuximab 100, 50 mg	Colorectal cancer	Merck	Feb 22, 2008 May 21, 2008	Rejection	Submitted	Not listed: Australia, UK
Vorina inj. 2.5%	Sodium folinate 100, 300 mg	Leukemia as an adjuvant	Myungji Pharm	Jan 25, 2008 Sep 26, 2008	Rejection	n/s	Germany
Faslodex	Fulvestrant 250 mg/5 mL	Metastatic breast cancer	Astra Zeneca Korea	Apr 25, 2008 Sep 26, 2008	Rejection	Submitted	US, UK, Italy, France, Germany, Switzerland[a]
Nipent inj. 10mg	Pentostatin 10 mg	Hairy cell leukemia	DB Pharm Korea	Mar 19, 2009	Rejection	n/s	US, UK, Italy
Hycamtin	Topotecan HCl 0.27, 1.09 mg	SCLC	GSK Korea	Jun 18, 2009	Approval	n/s	US, UK, France, Germany
Tasigna	Nilotinib 200 mg	CML	Novartis Korea	Oct 28, 2008 Aug 20, 2009	Approval	Submitted	US, Australia, Switzerland
Tykerb	Lapatinib ditosylate 250 mg	HER2-positive breast cancer	GSK Korea	Jan 15, 2008 May 21, 2008 Nov 19, 2009	Approval	Submitted	US, France, Germany, Switzerland, UK, Australia[b]
Yondelis	Trabectedin 0.25, 1.0 mg	Soft tissue sarcoma	Janssen Korea	Jan 21, 2010 Mar 25, 2010	Rejection	n/s	UK, Germany, Italy

*CE, cost-effectiveness; n/s, not submitted; n/m, not mentioned; KODC, Korea Orphan Drug Center; CML, chronic myeloid leukemia; ALL, acute lymphoblastic leukemia; HER2, human epidermal growth factor receptor 2; SCLC, small cell lung cancer. [a]In all reference countries, the drug was approved and listed as a second-line treatment. [b]For Australia, pre-approval was required before using lapatinib

burden considering the sum of insurance expenditures and budget impact outcomes (although the explicit values were not stated on the PSDs), leading to positive final decisions as in the case of dasatinib.

Indeed, the inherent uncertainty in the economic models of DREC was often expressed in the PSDs. For example, in the PSDs with non-coverage decisions (such as cetuximab), lack of confidence in assumption or input data of economic modelling was stated as a causative factor, rather than the judgment being based on an explicit value like the ICER (Table 2). The fact that PBAC deliberated on cetuximab over seven meetings revealed that the complexity in economic modelling required time and back and forth endeavor to resolve specific technicalities in the HTA. However, the application of cetuximab was discussed only twice by DREC, after which it was rejected with no further deliberation allowed in the process of evaluating any empirical evidence.

Relevance of comparator selection: While best supportive care was admitted as a comparator of cetuximab, topotecan oral, and trabectidin by PBAC and NICE, none of new drugs were approved in DREC's appraisal if they were compared with best supportive care (Tables 2 and 3). Indeed, except dasatinib, no oncology drug was acknowledged as a medical necessity by DREC, and dasatinib was also approved by PBAC under the Rule of Rescue guideline.

The absence of direct comparison in clinical trials has often propelled the conclusion of insufficient and unclear clinical efficacy by DREC. However, there are often limited treatment options available for terminal cancers. For example, there had been no standard second- or third-line treatment indications when early clinical trials of cetuximab were designed (Table 2). Furthermore, because some cancers occur very rarely (such as hairy cell leukemia), it would be difficult to ever construct a trial on a large enough scale to substantiate a clinical improvement.

Some comparators determined by DREC were disputed by the interviewee oncologists. For example, imatinib 800 mg for the treatment of imatinib-tolerant patients and salvage therapy (S-1) of cetuximab as the comparator were considered unreasonable (Table 2). The assumption of trastuzumab continuation is also discordant with the actual care setting in Korea (Table 2). Furthermore, while asserting that trastuzumab cannot be the comparator for lapatinib, a contradictory statement was made in the PSD by DREC that the cost of lapatinib therapy was lower than the cost of trastuzumab.

Sometimes a technical solicitation of a "comparable" drug in economic modelling resulted in the selection of a comparator with less relevance. For example, PBAC did not consider bevacizumab as an appropriate comparator for cetuximab on the grounds that cetuximab therapy is more efficacious against K-RAS wild-type patients. However, the K-RAS type was unknown at the time when treatment commenced; thus, in reality, bevacizumab maintains its first-line treatment position and cetuximab is used for the treatment of bevacizumab failure (Table 2). The clinical efficacy of oncology drugs typically varies across patients, indicating there may be a marker for choosing a patient group in which the drug will show the best efficacy. While such a marker for bevacizumab is unfortunately unknown, cetuximab has one that appears to work. Currently, the choice of the interviewee oncologists between cetuximab and bevacizumab depends on K-RAS type, in addition to the patient's status in terms of gender and cardiovascular problems

Considering ethical aspects

Exceptional conditions for reimbursement: The ICER of trabectedin over best supportive care (£34,500/quality-adjusted life year) was approved with end-of-life criteria by NICE. However, it was rejected in the DREC decision by reason of non-submission of ICER figures (Table 3). Most of the oncologists interviewed thought that new drugs for rare cancers should be waived of economic evaluation for reimbursement decisions. Although these novel drugs are expensive, the budget impact of listing them will not be catastrophic from the insurer's perspective because the patient pool is exceptionally small. Nonetheless, in the DREC reports, there was no case among oncology drug applications which were exempt from economic analyses and which involved ethical considerations.

Some recently developed second- and third-line cancer drugs are for patients who have no other option due to failure of, intolerance to, or contraindication with the existing therapy. Indeed, even though the majority of patients may be treated with a first-line therapy, the second- and third-line treatment options need to be established in society for the treatment security of rare cancer patients. However, these drugs were likely to be rejected for coverage by reason of technical difficulties (such as lack of a clinical trial) or no submission of an ICER value with a particular comparator that was pre-determined by DREC.

Accountability about reviewers: DREC is the only committee to review all reimbursement applications submitted to HIRA. However, as there was no clear HIRA guideline for examination for ethical issues in the technology assessment, there was no ethics specialist among the committee members. Furthermore, neither oncologists nor cancer patient representatives were included in DREC reviewing these new oncology drugs. Without seeking expert advice and stakeholder's involvement, it would be hard to sufficiently reflect and convey the needs and values of the public in the technology assessment for new oncology drugs for reimbursement decisions. Indeed, HIRA seldom reported information about who had participated in meetings and potential committee member conflicts of interest on the PSDs.

Equity in the choice of reimbursable cancer drugs: Dasatinib was acknowledged for its clinical indispensability by DREC, but nilotinib was not. Decitabine was approved while its alternative, azacitidine, was available in the listing (Table 1). In contrast, pentostatin was rejected on the concern that it might increase financial burden by replacing cladribine, which was not even being reimbursed at that time (Table 1). However, there was no obvious

Table 2. Empirical Factors in DREC Decisions on Reimbursement Applications for Cancer Drugs Compared with PBAC Decisions

Evaluation point	DREC Decision	PBAC Decision
Dasatinib		
Recommendation	Approval (Jul 20, 2007) for both CML and ALL	Approval for CML (Mar 2007); approval for ALL (Jul2007)
No. of Meetings	One	One for CML, two for ALL
Medical necessity	Required	
Comparators	Imatinib 800 mg	Imatinib resistant: 800 mg/day. Imatinib intolerant: 300-400 mg/day
Clinical evidence	For imatinib-tolerant patients in CML phase, MCyR rate was higher at the median 15-month point. In ALL patients, 42% of ALL patients had major hematological responses.	For CML patients, dasatinib had significant advantages in effectiveness in terms of a complete cytogenetic response while the MCyR was not statistically significant at either the 12 wk or 1 yr time point. Study CA 180-015 showed evidence of rescue in a significant minority of patients.
Economic or BIA evidence	The 1-year cost of dasatinib was lower than the comparator.	Regarding CML, drug cost is high and the ICER is sensitive to the imatinib dose and the dasatinib price should be calculated considering dasatinib 140 mg is no greater than the price for imatinib 670 mg. Regarding ALL, the ICER range was $45,000 to $75,000. The listing of dasatinib for the small patient group was consistent with the 'Rule of Rescue' guideline.
Cetuximab		
Recommendation	Rejection (May 21, 2008)	Approval (Jul 2010)
No. of Meetings	Two	Seven
Medical necessity	Not for rare disease	
Comparators	Cetuximab+irinotecan vs. FOLFOX, CapeOX, S-1, or capecitabine	BSC
Clinical evidence	Study 007 trial: cetuximab vs. cetuximab+irinotecan: OS response (10.8% vs. 22.9%) was significant with no significant difference in survival time (8.6 vs. 6.9 months). However, no clinical trial data in comparison with other second-line chemotherapy was available.	Accepted with the evidence of the CO17 trial cetuximab+chemotherapy vs. BSC, FOLFOX, FOLFIRI, cetuximab+irinotecan, cetuximab+oxaliplatin. Bevacizumab is not an appropriate comparator.
Economic or BIA evidence	The assumption that both ASC and BSC had the same effectivenesswas not acceptable. Unclear cost-effectiveness for 2nd and 3rd line treatment of approved indication. In future, a model comparing with salvage therapy (S-1) should be developed.	The weighted ICER was between $45,000 and $75,000/QALY, which PBAC considered high but acceptable. The accuracy of K-RAS test should be assessed; this was being funded by the sponsor.
Topotecan oral		
Recommendation	Approval (Jun 18, 2009)	Rejection (Jul 2010)
No. of Meetings	Two	One
Comparators/ Medical necessity	Topotecan IV/Not necessary	BSC
Clinical evidence	Topotecan plus BSC improves overall survival and quality of life compared with BSC. No difference compared with topotecan IV.	Uncertain clinical benefit: the submission and clinical trial did not provide a well-defined inclusion criterion for "contraindication to CAV" and "patients for whom IV therapy is inappropriate" as the revised restrictions proposed by the sponsor according to pre-PBAC response.
Economic or BIA evidence	Topotecan cost for one cycle is lower than the comparator	The ICER was sensitive to the effect of male gender and the presence of liver metastases; $75,000 to $105,000/QALY for males and for less than $15,000/QALY for females. Thus, the ICER is high and uncertain.
Nilotinib		
Recommendation	Conditional approval (Aug 20, 2009)	Approval (Mar 2008)
No. of Meetings	Two	One
Comparators/ Medical necessity	Dasatinib, high-dose imatinib/Not necessary	Dasatinib, high-dose imatinib
Clinical evidence	No clinical data on direct comparison. Also, clinical trials used different definitions for imatinib intolerance, and thus, the data were not useful.	For the chronic phase, both nilotinib and dasatinib are highly effective. However, because the data did not come from a single trial, it was difficult to say which one was better. For accelerated phase, insufficient data to conclude its non-inferiority.
Economic or BIA evidence	ICER value was not cost-effective. The drug therapy cost was higher than comparators for chronic phase while it was lower for accelerated phase. The price as a weighted average of comparators' prices was accepted.	Cost minimization analysis (the equi-effective dose: nilotinib 800 mg vs. dasatinib 140 mg).
Lapatinib		
Recommendation	Approval (Nov 19, 2009)	Approval (Nov 2007). For lapatinib continuation beyond progression, a risk-share arrangement is recommended.
No. of Meetings	Three	Two
Comparators/ Medical necessity	Capecitabine monotherapy, gemcitabine+vinorelbine/Not necessary	Capecitabine, trastzumabmonotherapy, trastzumab+vinorelbine, trastzumab+capecitabine, trastzumab+taxane, gemcitabine+taxane.
Clinical evidence	Effective for CNS metastases, Lapatinib+capecitabine has been used without reimbursement in practice.	The conservative assumption that trastzumab continuation was at least as effective as lapatinib+capecitabine was accepted.
Economic or BIA evidence	Lower costs for patients whose tumors overexpress HER2 and have progressedafter treatment with trastuzumab. Also less expensive than the trastuzumab therapy. The ICER compared capecitabine monotherapy or emcitabine+vinorelbine for advanced/metastatic breast cancer patients, which was acceptable.	The ICER was extremely sensitive to the rate of lapatinib for continued treatment with trastuzumab and the sponsor's price offer with a 50% rate of substitution of trastzumab resulted in an ICER of $45,000 to $75,000.

*ALL, acute lymphoblastic leukemia; ASC, active supportive care; BIA, budget impact analysis; BSC, best supportive care; CAV, cyclophosphamide + doxorubicin + vincristine; CapeOX, capecitabine + oxaliplatin; CML, chronic myeloid leukemia; CNS, central nervous system; DREC, Drug Reimbursement Evaluation Committee; FOLFIRI, folinic acid + fluorouracil + irinotecan; FOLFOX, folinic acid + fluorouracil + oxaliplatin; HER2, human epidermal growth factor receptor 2; ICER, Incremental

Table 3. Evidentiary Factors in DREC Decisions on Reimbursement Applications for Cancer Drugs Compared with NICE Decisions

Evaluation point	DREC Decision	PBAC Decision
Fulvestrant		
Recommendation	Rejection (Sep 26, 2008)	In progress (issue date: Aug 2010) Currently listed as 2nd line therapy
No. of Meetings	Two	
Medical necessity	Exemestane/Not necessary	Anastrozole, exemestane, letrozole
Clinical evidence	While clinical guideline suggests this drug therapy for 2nd line, its approval is for 3rd line therapy about which no clinical trial had been conducted.	Endocrine therapy is appropriate for about 70% of hormone receptor-positive advanced breast cancer patients.
Economic or BIA evidence	ICER shows uncertain cost-effectiveness. The costs during median TTP (3 months) were higher than the costs of exemestane.	
Trabectedin		
Recommendation	Rejection (Mar 25, 2010)	Approval (Feb 2010)—review date (Feb 2013)
No. of Meetings	Two	
Comparators/ Medical necessity	Gemcitabine + docetaxel/Not necessary; no alternative registered for the same indication, but gemcitabine + docetaxel could be used clinically.	BSC/soft tissue sarcoma is a rare condition and there is no licensed treatment option apart from trabectedin.
Clinical evidence	No clinical data on direct comparison. Uncertain clinical effectiveness for trabectedin (RR: 5.6%; TTP: 3.7 months) compared with gemcitabine+ docetaxel (RR: 17%; PFS: 6.2 months) in comparison with gemcitabine.	Patients with the licensed dose of trabectedin showed better PFS than patients with an active regimen of BSC.
Economic or BIA evidence	Drug cost for 1 cycle is expensive and the price was greater than the weighted average price of other countries. Difficult to determine the weighted average cost of the comparator because gemcitabine+docetaxel therapy is not standardized, requiring permission before use.	The ICER of £34,500/QALY in the light of the end-of-life criteria was within the current threshold range and acceptable.

*BIA, budget impact analysis; BSC, best supportive care; DREC, Drug Reimbursement Evaluation Committee; ICER, incremental cost effectiveness ratio; NICE, National Institute for Health and Clinical Excellence; PFS, progression-free survival; RR, risk ratio; TTP, time to progression; QALY, quality-adjusted life year

guideline for these decisions, but rather these depended on the interpretation of evidence by DREC and the dynamics of pharmaceutical markets.

Recently, the plan to re-evaluate approximately 20,000 listed drugs was rescinded in Korea, resulting in a price cut en bloc for all listed drugs rather than reducing the number of listed drugs. It is difficult to sort out disposable drugs among competitors on the national drug formulary. Further, especially when two new drugs are on par with one another in terms of both clinical and economic outcomes (such as dasatinib and nilotinib), the decision to reimburse only one should be justified and assured to the public. However, there has been no discussion about fairness for applying economic evaluation hurdles only to new drugs developed from the time when the HTA system was been implemented in 2007.

Publicity of decision processes and rationales: Because the figures of ICER values or the drug prices evaluated by DREC have been redacted from the PSDs, it is not possible for the public to make value judgments based on missing numerical evidence. On the contrary, this information is disclosed in the reports of PBAC and NICE. The aim of publishing the PSDs was to explain the decision results and the reasoning of the committee to the public. No matter the reasons for non-disclosure, it may be contradictory that the public is expected to judge and trust a decision based on economic evidence that is not provided to the public.

While privileging the primary data relevant to the Korean healthcare system in drawing cost-effectiveness evidences, however, HIRA has not made public much empirical data, such as budget figures and utilization amounts, which are under the jurisdiction of HIRA itself (Health Insurance Review and Assessment Service: HIRA, 2007). Indeed, the interviewee oncologists agreed that if HIRA shared utilization and expenditures information, those unanswered assumptions in the HTA submissions would be properly questioned and considered.

Discussion

This paper has presented the pitfalls of the HTA-based Korean centralized prescription drug review policy for reimbursement decisions. Many of the rationales and empirical evidences used in deriving decisions for oncology drugs by DREC were not agreed upon because of the lack of clear relevance, despite all of the information the PSDs contained. Moreover, reimbursement policies for cancer drugs in Korea have not been sufficiently accessible to the public in a timely manner. Evidentiary factors were not consistently applied to listing decisions and were not recorded on the PSDs of the DREC. The information related to the process and reviewers of the HTA were seldom delineated on the PSDs either, preventing the publicity of reimbursement decisions and their rationale. Because of the hasty adoption of the HTA evaluation, there may have been a delay in paying particular attention to constructing detailed manuals and concrete processes for assessing HTA reports, as well as for rendering recommendation decisions public for accountability.

Furthermore, we found that normative and ethical values about new oncology drugs were rarely evaluated. Indeed, by focusing on economic and clinical evidence, the evaluation system in Korea has neglected the ethical issues which are intrinsic attributes of HTAs. Economic evaluation with cost-effectiveness analysis originated from utilitarian theory, and accordingly, policy decisions based on cost-effective evidence would reimburse a drug which then maximizes its average utility among the society. In the view of utilitarianism, decisions motivated by societal

duty or sympathy rather than those being grounded on scientific evidence infringe on allocative efficiency. However, considering that both utilitarian and moral behaviours have the same goal (which is the production of maximal utility), it would not be an incongruous work to examine both cost-effectiveness and ethical aspects altogether in drug reimbursement assessment (Pinkerton, 2002). The social benefit arises from an improvement of citizens' health per se, but it should be further increased by reinforcing the belief that they live in a system that cares their life and accepts their priorities (McKie and Richardson, 2003).

Because ethics has only recently been emphasized as a part of the HTA, little consensus had been made on the methods for incorporating ethics into HTA systems (Hofmann, 2008; Burls et al., 2011). Final decisions could be different across different HTA systems because a drug could have different economic or ethical values depending on the society. However, if the decision-making was brought forth based on rational evidence that included both empirical and ethical concerns, and if the decision-making process was indeed a fair evaluation procedure open to the public, then it likely would gain universal acceptance. In this sense, procedural justice may be the most prominent feature to consider in policy-making, because although not infallible, it is certainly the best procedure generally acceptable to the society (Abelson et al., 2007; Droste et al., 2010). Thus, transparent criteria at all decision stages and an explicit discussion of formal criteria and procedures are essential for accountable policy-making. Norman Daniels' theory "Accountability for Reasonableness" suggests four conditions aimed at solving policy decision problems that involve legitimacy and fairness: Condition i, publicly accessible rationales; Condition ii, reasonableness or relevance on rationales; Condition iii, dispute resolution procedures; and Condition iv, voluntary or public regulation (Daniels and Sabin, 1997).

Regarding these four conditions, our research shows that the overall criteria of publicity and reasonable rationale in the review for reimbursement decisions have not been met. Ethical values about each new oncology drug have not been sufficiently sought. Furthermore, appropriate communication of the evidence should include clinicians, patients, and the general public in the future (Drummond et al., 2009; Oortwijn et al., 2010). Efforts of being ready to be accountable for the policy decisions and their rationales are called for if the ethics of reimbursement decisions is worth considering in Korea. Indeed, without the concept about fairness in policy decisions, the public is unlikely to accept any decisions even they are in fact reasonable (Daniels et al., 2003).

In drawing the results of this study, the essential features of the PSDs may not have been overtly specified by the authors. However, the qualitative analysis and review by the investigators on the clinical, economic, and ethical aspects of decisions and the evaluation process for each new oncology drug noted in the PSDs makes it possible for the present study to incorporate extensive insights on ethical concerns that are lacking in the current HTA policy. Although not representing the entire society for the value of oncology drugs, the oncologists invited in the analytical discussion had provided expertise on the empirical evidence as well as opinions about what was missed in terms of the ethical values throughout DREC's reimbursement decisions for oncology drugs in Korea.

The reimbursement decision-making for oncology drugs needs to be improved in consideration of the ethical aspects of the HTA-based policy in Korea. Decisions should be based on empirical evidence with clear relevance which is agreed upon by the public. Ethical values should be addressed for each of the new drugs. Most of all, encompassing the public accountability for reasonableness toward the decisions and the rationales is certainly required for fair limit-setting policy on oncology drug treatments.

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